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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,748	11/30/2004	So H. Lee	5806SNU-1	7184

22442 7590 04/14/2009

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ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
04/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,748	LEE ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 01/23/2009 has been entered. Claims 1-8 and 13 are cancelled. Claims 9, 10, and 12 are amended. Claims 9-12 are currently under examination.

This application 10/500,748 is a 371 of PCT/KR01/02304, filed on 12/29/2001

Claim Objections

1. Previous objection of claim 9 for recitation of the limitation "GeneBank Accession NO.: AF221517", is ***withdrawn*** because this limitation has been deleted.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Indefiniteness

2. Previous rejection of claims 9-12 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because the claims have been amended.

Claim 9 has been amended and no longer recites the following phrase (i) "a normal GT protein" in line 12, (ii) "through a PCR method using primers prepared based on a pig GT cDNA sequence (GenBank Accession NO.: AF221517)", and (iii) "wherein the gene targeting vector at the step (b) comprises a nucleic acid sequence *corresponding to* a part of intron 8, exon 9 and a part of intron 9 of a GT gene, wherein an AvaI-DraIII fragment of said exon 9 is substituted with

a nucleic acid sequence encoding a puromycin-resistant gene linked to an SV 40 poly (A) sequence". Claim 10 depends from claim 9.

The rejection of claims 11 and 12 are withdrawn because claims 11 and 12 have been amended as independent claims and no longer depend from claim 9.

3. Claims 9 and 10 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed by applicant on 01/23/2009.*

Amended claim 9 recites "(b) isolating an alpha-1, 3-galactosyltransferase (GT) gene clone from a pig genomic BAC library and constructing a gene targeting vector comprising a nucleic acid sequence consisting of a part of intron 8, exon 9 and a part of intron 9 of a GT gene, wherein an AvaI-DraIII fragment of exon 9 is substituted with a nucleic acid sequence encoding a puromycin-resistant gene linked to an SV 40 poly (A) sequence;". The phrase "isolating an alpha-1, 3-galactosyltransferase (GT) gene clone from a pig genomic BAC library" indicates the GT gene is a pig GT gene. However, the phrase "constructing a gene targeting vector comprising a nucleic acid sequence consisting of a part of intron 8, exon 9 and a part of intron 9 of *a GT gene*" reads on any GT gene from any species with any variations. As two different scope of GT gene is recited in the same step of claim 9, the metes and bounds of the claim cannot be determined. As a related issue, the specification is unclear whether the limitation "AvaI-DraIII fragment of exon 9" is conserved in all GT genes or it is specifically present in the

pig GT gene isolated from the recited pig genomic BAC library. Claim 10 depends from claim 9.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

4. Previous rejection of claims 9-12 under 35 U.S.C. 112, first paragraph, is ***withdrawn*** because the claims have been amended. Previous scope of enablement rejection indicates that the specification, while being enabling for a method of producing a cloned pig having an alpha-l,3-galactosyltransferase gene knocked out, comprising the steps of: preparing a nuclear donor cell by culturing *a porcine fetal fibroblast cell* (b) isolating an alpha-1,3-galactosyltransferase (GT) gene clone from *a pig genomic library*, and constructing a gene targeting vector using the isolated GT gene, wherein the vector carries a GT gene modified by substituting a portion of a GT gene with a gene encoding a selectable marker by homologous recombination to suppress expression of *an endogenous GT gene*; (c) mixing the vector with a lipid or non-lipid component to form lipid (or non-lipid)-DNA complexes, and adding the resulting complexes to a culture medium of the nuclear donor cell to allow gene targeting by introducing the recombinant GT gene into the nuclear donor cell to produce a transfected nuclear donor cell; (d) transferring the transfected nuclear donor cell with the recombinant GT gene into an enucleated pig recipient oocyte to generate a transgenic nuclear transfer embryo, and activating the nuclear transfer

embryo; and (e) transplanting the activated nuclear transfer embryo into a surrogate mother pig to produce live offspring, wherein the gene targeting vector at the step (b) comprises the nucleic acid sequence of a part of intron 8, exon 9 and a part of intron 9 of a GT gene, wherein exon 9 comprises an AvaI-DraIII fragment, and wherein the AvaI-DraIII fragment of said exon 9 is substituted with a nucleic acid sequence encoding a puromycin-resistant gene linked to an SV 40 poly(A) sequence, **does not** reasonably provide enablement for (1) any porcine somatic cells other than a fetal fibroblast cell, (2) any PCR method used to generate the claimed AvaI-DraIII fragment of said exon 9, and (3) any non-viable "SNU-P2 [Porcine NT Embryo]" used for nuclear transfer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The aspect of the rejection pertaining to any porcine somatic cells other than a fetal fibroblast cell is ***withdrawn*** because claim 9 has been amended to recite "a fetal fibroblast cell line collected from a pig". Claim 10 depends from claim 9.

The aspect of rejection pertaining to any PCR method used to generate the claimed AvaI-DraIII fragment of said exon 9, is ***withdrawn*** because claim 9 has been amended and no longer recites the limitation "through a PCR method using primers prepared based on a pig GT cDNA sequence (GenBank Accession No.: AF221517)". Claim 10 depends from claim 9.

The rejection of claims 11 and 12 pertaining to any non-viable "SNU-P2 [Porcine NT Embryo]" used for nuclear transfer, is ***withdrawn*** because claim 11 and 12 have been amended

to be independent claims. However, a new lack of enablement is by the claim amendments filed on 01/23/2009, see below.

5. Claims 11 and 12 newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *This rejection is necessitated by the claim amendments filed on 01/23/2009, which amend claims 11 and 12 as independent claims.*

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Claims 11 and 12 are rejected based on the requirements for deposit of biological materials. The reasons of this new rejection are the same as those documented on pages 12-13 of the office action mailed on 07/23/2008.

The application contains a porcine nuclear transfer embryo "SNU-P2 [porcine NT embryo]" (claims 11 and 12 of instant application), that is encompassed by the definitions for biological material set forth in 37 C.F.R. § 1.801. The specification teaches "SNU-P2 [Porcine NT Embryo]". As "SNU-P2 [Porcine NT Embryo]" is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If "SNU-P2 [Porcine NT Embryo]" is not so obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make" may be satisfied by a deposit of "SNU-P2 [Porcine NT Embryo]". The specification does not disclose a repeatable process to obtain "SNU-P2 [Porcine NT Embryo]" and it is not apparent if it is readily available to the public. If the deposit is to be made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating "SNU-P2 [Porcine NT Embryo]" has been deposited under the Budapest Treaty and that "SNU-P2 [Porcine NT Embryo]" will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:(a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request; (b) all

restrictions upon availability to the public will be irrevocably removed upon granting of the patent; (c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,

(d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become inviable.

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention.

Applicant's Arguments

Applicant argues that a declaration by the Applicant of deposit of SNU-P2[Porcine NT Embryo] with the Korean Collection for Type Cultures (KCTC) which is an International Depositary Authority (IDA) recognized under the Budapest Treaty in compliance with 37 CFR § 2405. Applicant argues that in light of this deposit and Applicants' declaration, the recitation ofSNU-P2 [Porcine NT Embryo] is enabled.

Response to Applicant's Arguments

The Declaration filed by Applicant on 01/20/2009 is deposited is acknowledged. It is noted that the specification discloses that the deposit of SNU-P2[Porcine NT Embryo] was made on 12/27/2001 (See paragraph [0051], US 2005/0076399, publication od instant application), which meets the requirement under 37 CFR 1.809(d), the specification shall contain: (1) the accession number for the deposit; (2) the date of deposit; (3) a description of the deposited

biological material sufficient to identify it and to permit its examination; and (4) the name and address of the depository. However, the declaration is defective in the following two aspects. First, the declaration does not state "SNU-P2 [Porcine NT Embryo]" will be irrevocably and without restriction released to the public upon the issuance of a patent". Second, in light of the deposited biological material being an embryo, Applicant is advised to provide statements on the record regarding a test of viability of the biological material at the time of deposit, and the deposit will be replaced if it should ever become inviable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 9 and 12 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Day et al.** (US publication NO 2005/0120400, publication date, 06/02/2005, effective filing date 12/21/2001) in view of **Mason et al.** (US patent 5,576,201, issued 11/19/1996). Applicant's arguments filed 01/23/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 16-20 of the office action mailed on 07/23/2008.

Claim 9 has been amended to read as follows: A method of producing a cloned pig having an alpha-1,3-galactosyltransferase gene knocked out, comprising the steps of:(a)

preparing a nuclear donor cell by culturing a fetal fibroblast cell line collected from a pig; (b) isolating an alpha-1,3-galactosyltransferase (GT) gene clone from a pig genomic BAC library, and constructing a gene targeting vector comprising a nucleic acid sequence consisting of a part of intron 8, exon 9 and a part of intron 9 of a GT gene, wherein an AvaI-DraIII fragment of exon 9 is substituted with a nucleic acid sequence encoding a puromycin-resistant gene linked to an SV 40 poly(A) sequence; (c) mixing the vector with a lipid or non-lipid component to form lipid (or non-lipid)- DNA complexes, and adding the resulting complexes to a culture medium of the nuclear donor cell to allow gene targeting by introducing the recombinant GT gene into the nuclear donor cell; (d) transferring the nuclear donor cells transfected with the recombinant GT gene into an enucleated pig recipient oocyte to generate a transgenic nuclear transfer embryo, and activating the nuclear transfer embryo; and (e) transplanting the nuclear transfer embryo into a surrogate mother pig to produce live offspring that do not have alpha-l,3-galactosyltransferase protein activity.

Claim 12 has been amended on 01/23/2009 to read as follows: A cloned pig having an alpha-l,3-galactosyltransferase gene knocked out, which is produced by the method comprising: transferring an SNU-P2 [Porcine NT Embryo] into an enucleated pig recipient oocyte to generate a transgenic nuclear transfer embryo, and activating the nuclear transfer embryo; and transplanting the nuclear transfer embryo into a surrogate mother pig to produce live offspring that do not have alpha-1,3-galactosyltransferase protein activity. It is noted that "SNU-P2 [Porcine NT Embryo]" recited in currently amended claim 12 is made by the step (c) of claim 9. This is evident by the disclosure in the specification (See paragraph [0051], US 2005/0076399,

publication of instant application) as well as by the recitation of previous version of claim 9 filed on 03/26/2008.

For clarity and completeness of this office action, previous rejection for the reasons of record advanced on pages 16-20 of the office action mailed on 07/23/2008 is reiterated below, with revisions to address claim amendments filed on 01/23/2009.

Claim interpretation: Claim 12 as amended is a "product by process" claim. However, for art rejection, the process (i.e., the recited method steps) bear limited, if any, patentable weight because it does not impart a difference in cloned pig having an alpha-l, 3-galactosyltransferase gene knocked out.

Day et al. teaches methods for making viable gene knockout swine in which the alpha (1, 3)-galactosyltransferase gene has been disrupted (See abstract, Figure 3, Day et al., 2005). The method steps taught by Day et al. render the steps recited in claim 9 obvious.

With regard to method step pertaining to preparation of nuclear donor cell (step (a) of claim 9), Day et al. teaches that the donor cell is a primary fibroblast (See paragraph [0030], Example 1, Day et al., 2005).

With regard to method step pertaining to isolation of alpha (1, 3)-galactosyltransferase gene clone (step (b) of claim 9), Day et al. teaches GalGT targeting vector and genomic PCR assays for targeting. The structure of the region of the alpha (1, 3)-galactosyltransferase (GGTA1) locus beginning with exon 7 is depicted (scale in kilobase pairs). GGTA1 homologous sequences in the pGalGT vector begin about 0.8 kb downstream of exon 7 and continue to about 6.8 kb downstream of the end of exon 9. A selection cassette, consisting of a Bip internal ribosome entry site, APRT coding sequences (encoding G418 resistance) and

flanking stop codons, is inserted into an *Eco* RV site upstream of the GGTA1 catalytic domain in exon 9 (See Figure 1, Day et al., 2005). It is noted that in the absence of disclosure of specific sequences of "an AvaI-DraIII fragment of exon 9" recited in step (b) of claim 9 of instant application, the disclosure by Day et al. regarding insertion of APRT coding sequences (encoding G418 resistance) in exon 9 of a pig GT gene renders the limitation "an AvaI-DraIII fragment of exon 9 is substituted with a nucleic acid sequence" recited in claim 9 of instant application (See diagram in Figure 9 of instant application) obvious.

With regard to step pertaining to gene targeting by introducing the recombinant GT gene into the nuclear donor cell (step (c) of claim 9), Day et al. teaches that approximately $2x10^7$ fibroblasts were electroporated at 260 V, 960 uFD in 0.8 ml of Hepes buffered saline containing 0.5 pmol/ml of pGalGT. The vector was restriction digested at both ends of the GGTA1 homologous sequences prior to use. Transfected cells were cultured in bulk for 2 days without selection, then plated in collagen-coated 96 well plates at $2 x10^4$ cells per well in Ham's nutrient mixture F10-20% fetal bovine serum (FBS) containing 100 μg/ml G418 (See paragraph [0061], Day et al., 2005). These disclosures by Day et al. teach "mixing the vector with non-lipid component to form non-lipid-DNA complexes and adding the complexes to a culture medium of nuclear donor cell" recited in step (c) of claim 9 of instant application.

With regard to step pertaining to transplanting the nuclear donor cells transfected with the recombinant GT gene into an enucleated pig recipient oocyte (step (d) of claim 9), Day et al. teaches the nuclear transfer of transfected donor fibroblast cells into enucleated oocytes (See Example 2, paragraph [0066], Day et al., 2005).

With regard to step pertaining to transplanting the nuclear transfer embryo into a surrogate mother pig to produces live offspring that do not have alpha (1, 3)-galactosyltransferase (step (e) of claim 9), Day et al. teaches transplantation of nuclear transfer (NT)-derived embryos to mated surrogates (See Example 3, paragraph [0066]-[0070], Day et al., 2005), and transplantation of nuclear transfer (NT)-derived embryos to unmated surrogates (See Example 4, paragraph [0071], Day et al., 2005).

With regard to claim 12, the claim is a product-by-process claim reciting the cloned pig is produced transferring an SNU-P2 [Porcine NT Embryo] into an enucleated pig recipient oocyte to generate a transgenic nuclear transfer embryo, and activating the nuclear transfer embryo; and transplanting the nuclear transfer embryo into a surrogate mother pig to produce live offspring that do not have alpha-1, 3-galactosyltransferase protein activity. In this regard, Day et al. teaches viable gene knockout swine including swine in which the alpha (1, 3)-galactosyltransferase gene has been disrupted; methods for making such swine (See abstract, Figure 3, Day et al., 2005). Since the cloned pigs are claimed as product-by-process, applicant bears the burden to provide evidence that distinguishes the claimed products over those known in the prior art at the time of filing.

[E]ven though product-by-process claims are limited by and defined by the process; determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

"The Patent Office bears a lesser burden of proof in making out a case of prima facie

obviousness for product-by-process claims because of their peculiar nature" than when a product is claimed in the conventional fashion. In re Fessmann, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983).

"Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product (*In re Ludtke*). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972))."

"When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934.) See MPEP 2113 and MPEP 2112.01.

However, Day et al. does not teach a vector with puromycin-resistant gene linked to an SV40 poly (A) sequences recited in step (e) of claim 9 of instant application.

Mason et al. teaches a transducing vector with puromycin-resistant gene linked to a SV40 poly (A) sequences (See Figure 3, Mason et al., 1996).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Day et al. and Mason et al. to arrive at the claimed method of producing a cloned pig having an alpha (1,3)-galactosyltransferase gene knocked out.

One having ordinary skill in the art would have been motivated to combine the teachings of Day et al. and Mason et al. because both puromucin and G418 are commonly used selection marker used for select cells that have been transfected with target DNA vector, and SV40 poly (A) sequences is commonly used in a vector for proper expression of cloned gene of interest.

There would have been a reasonable expectation of success given (i) successful generation of a cloned pig which the alpha (1,3)-galactosyltransferase gene has been disrupted, (ii) demonstration of transducing vector that harbors puromycin-resistant gene linked to an SV40 poly(A) sequences. The ordinarily skilled artisan would be well-versed and knowledgeable in various vectors that could be used in transfecting cells, because these techniques would be well within the skills of the ordinary artisan.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments

Applicant argues that the vector of Day interposes a selection marker gene of G418 tolerance between exons 7 to 9 of a pig GT gene to knockout the GT gene. Therefore, using the vector of Day, live offspring from which exons 7 to 9 are removed are obtained. Applicant

argues that, in contrast to the methods of Day, the gene targeting vector construct of the subject invention contains a nucleic acid sequence corresponding to a part of intron 8, exon 9 and a part of intron 9 of a GT gene, and a nucleic acid sequence encoding a puromycin-resistant gene, wherein the puromycin-resistant gene substitutes a nucleic acid sequence corresponding to an AvaI-DraIII fragment of the exon 9. Applicant states that, in this targeting vector, the puromycin-resistant gene is inserted in exon 9 of the GT gene by homologous recombination of the homologous fragment, thereby disrupting the GT gene construction and result in substantially different effects, and the cloned embryos or the transgenic cloned pigs that are produced by the introduction of each of these vectors also have substantially different phenotypes. Applicant argues that the vectors of Day result in live offspring consisting of genes from which exons 7, 8 and 9 are removed, but in the instant invention, live offspring consisting of genes from which exon 9 is removed are produced. Thus, Applicant argues the live offspring of the two inventions have substantially different genotypes that result in different phenotypes (See pages 6-7 of Applicant's remarks file don 01/23/2009).

Applicant further argues that because the GT gene is inserted into a genome randomly even if an organ- specific promoter is used, it might not be expressed selectively only in a desired organ. Applicant states that, to solve this problem, an organ-specific transgenic pig is produced using a BAC (bacterial artificial chromosome) clone, and the BAC clone includes a promoter or an enhancer part that can be neglected, allowing the vector to reflect the nature of the original promoter. Applicant argues that, therefore, the subject invention obtains a GT gene clone of a desired size by screening a BAC genomic library pool, which is dramatically differently from that of Day, which is obtained from the entire genome of a pig. Applicant argues

that the subject invention therefore may be used to produce an organ specific transgenic pig, which is a significant advance over the disclosure of Day (See page 7 of Applicant's remarks file don 01/23/2009).

Applicant argues that Mason discloses a transgenic vector containing puromycin-resistant gene linked to a SV40 poly(A) sequence. However, the instant invention is directed to the removal of a GT gene from a cell that proliferates actively, while Mason teaches the introduction of a specific gene into a non-dividing cell like a nerve cell. Therefore, Applicant argues that one of skill in the art would not supplement the teachings of Day nor the vectors and methods of the instant invention with the vector constructs of Mason as they are directed to entirely different purposes.

Response to Applicant's arguments

As stated in the maintained rejection, Day et al. discloses a selection cassette, consisting of a Bip internal ribosome entry site, APRT coding sequences (encoding G418 resistance) and flanking stop codons, is inserted into an *Eco* RV site upstream of the GGTA1 catalytic domain in exon 9 (See Figure 1, Day et al., 2005). It is noted that in the absence of disclosure of specific sequences of "an AvaI-DraIII fragment of exon 9" recited in step (b) of claim 9 of instant application, the disclosure by Day et al. regarding insertion of APRT coding sequences (encoding G418 resistance) in exon 9 of a pig GT gene renders the limitation "an AvaI-DraIII fragment of exon 9 is substituted with a nucleic acid sequence" recited in claim 9 of instant application obvious. It is unclear to the Examiner with respect to the reasons why Applicant asserts that the vectors of Day (Figure 1, Day et al.) result in live offspring consisting of genes from which exons 7, 8 and 9 are removed, but in the instant invention, live offspring consisting

of genes from which exon 9 is removed are produced. To the Examiner's best knowledge of homologous recombination, the construct disclosed by Day et al. in Figure 1 will lead to disruption of exon 9 due to insertion of G418 resistant gene via homologous recombination mediated by flanking sequences of exons 7 and 8 at 5' end and part of exon 9 at 3'end, which is obvious over the construct claimed by step (b) of claim 9 reciting "wherein an AvaI-DraIII fragment of exon 9 is substituted with a nucleic acid sequence encoding a puromycin-resistant gene". The only differences appears to be that the construct taught by Day et al. leads to reading frame shift of exon 9 (thereby encoding totally different amino acid residues) downstream of the insertion site of the G418 resistant gene without physical deletion of exon 9 sequences whereas the construct claimed by instant application remove part of exon 9 and replaces it with a puromycin-resistant gene. Moreover, even if Applicant's assertion about how homologous recombination works were correct that most sequences of exons 7, 8 and 9 are removed using Day's construct, the limitation "a part of intron 8, exon 9 and a part of intron 9 of a GT gene" recited in step (b) of claim 9 reads on "any part of intron 8, exon 9 and any part of intron 9 of any GT gene".

As discussed in the preceding paragraph, the genotype of the cloned pig having an alpha-1, 3-galactosyltransferase gene knocked out claimed by instant application is obvious over the genotype of the cloned pig having an alpha-1, 3-galactosyltransferase gene knocked out disclosed by Day et al. because there is only a slight difference with regard to the exact construct and sequences pertaining to how exon 9 of pig GT gene is disrupted at molecular level. With regard to the asserted difference in phenotype, Applicant does not provide any evidence in this regard, and the claims of instant application do not recite any specific phenotype. This is not

persuasive. The arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01. Applicants have not provided an appropriate affidavit or declaration supporting that using Applicants' disclosed vector would result in an animal with a substantially different genotype that would result in a different phenotype. The phenotype of the claimed pig and that of Day is that there is no alpha-1, 3 galactosyltransferase protein activity. This is all that is required by the claim, and the combination of the cited art reasonably arrives at this phenotype.

With regard to the arguments that the how Applicant isolates the pig GT gene from a BAC library and what Applicant's intended use of the isolated GT gene is, the Examiner notes that there is no evidence on the record demonstrating that the pig GT gene isolated from a BAC library by instant application is in any way different from the GT gene isolated from a pig genomic library disclosed by Day et al. Moreover, the sequences and characteristics of the pig GT gene are not affected by the intended uses.

It is noted that the second reference by Mason is relied on for the disclosure regarding a transgenic vector containing puromycin-resistant gene linked to a SV40 poly (A) sequence. The teachings by Mason regarding introduction of a specific gene into a non-dividing cell like a nerve cell does not negatively affect the relevance of the disclosure by Mason regarding a transgenic vector containing puromycin-resistant gene linked to a SV40 poly(A) sequence to instant application. As documented in the maintained rejection, one having ordinary skill in the art would have been motivated to combine the teachings of Day et al. and Mason et al. because both puromucin and G418 are commonly used selection marker used for select cells that have

been transfected with target DNA vector, and SV40 poly (A) sequences is commonly used in a vector for proper expression of cloned gene of interest.

7. Claim 10 remains rejected under 35 U.S.C. 103(a) as being unpatentable over **Day et al.** (US patent publication 2005/0120400, publication date, 06/02/2005, effective filing date 12/21/2001) in view of **Mason et al.** (US patent 5,576,201, issued 11/19/1996) as applied to claim 9 above, and further in view of **Zhao et al.** (US patent publication 2003/0092070, publication date, 05/15/2003, effective filing date 08/30/2001). Applicant's arguments filed 01/23/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 20-22 of the office action mailed on 07/23/2008.

For clarity and completeness of this office action, previous rejection for the reasons of record advanced on pages 16-20 of the office action mailed on 07/23/2008 is reiterated below, with updated status of the rejection.

The teachings of Day et al. and Mason et al. have been discussed in the preceding section of the maintained rejection of claims 9 and 12 under 35 U.S.C. 103(a) as being unpatentable over Day et al. (US publication NO 2005/0120400, publication date, 06/02/2005, effective filing date 12/21/2001) in view of Mason et al. (US patent 5,576,201, issued 11/19/1996).

Neither Day et al. nor Mason et al. teaches FuGENE6 used for transfection as recited in claim 10.

Zhao et al. teaches DNA was transfected into each well using Fugene6 (Roche) following manufacture's protocol (See paragraph [0100], Zhao et al., 2003).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Zhao et al. on the use of FuGENE6 for transfection, into the combined teachings of Day et al. and Mason et al. directing to a method of generation of a cloned pig which the alpha (1, 3)-galactosyltransferase to arrive at claim 10 of instant application.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Zhao et al. into the combined teachings of Day et al. and Mason et al. because FuGENE6 is commonly used to enhance the DNA transfection efficiency.

There would have been a reasonable expectation of success given (i) successful demonstration of a method of generation of a cloned pig which the alpha (1,3)-galactosyltransferase by combined teachings of Day et al. and Mason et al., (ii) successful demonstration of enhanced DNA transfection into Hela cells by the teachings of Zhao et al. It is further noted that utilizing various transfection reagents, such as FuGENE6 would be well-within the capabilities of the ordinarily skilled artisan.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments

Applicant argues that Zhao is cited for the disclosure of the use of FuGENE6 for transfection, but the disclosure of Zhao does not overcome the lack of motivation and the shortcomings of the teaching of the combination of Mason and Day described above. Therefore, Applicants argues that there is no suggestion or motivation in the Mason and Day references to make the combination described by the Examiner.

Response to Applicant's arguments

The arguments pertaining to Day et al and Manson have been addressed in the maintained rejection of claims 9 and 12 under 35 U.S.C. 103(a) as being unpatentable over Day et al. in view of Mason et al. The reference by Zhao is relied on for the disclosure of the use of FuGENE6 for transfection. As stated in the maintained rejection, one having ordinary skill in the art would have been motivated to incorporate the teachings of Zhao et al. into the combined teachings of Day et al. and Mason et al. because FuGENE6 is commonly used to enhance the DNA transfection efficiency.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you

would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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